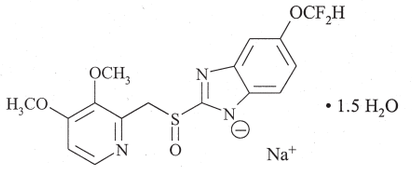
PROTONIX®

(pantoprazole sodium)

Delayed-Release Tablets

DESCRIPTION

The active ingredient in PROTONIX® (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$ x 1.5 H_2O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX is supplied as a delayed-release tablet for oral administration. Each delayed-release tablet contains 45.1 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg pantoprazole) with the following inactive ingredients: anhydrous sodium carbonate NF, mannitol USP, crospovidone NF, povidone USP, calcium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, yellow iron oxide NF, propylene glycol USP, methacrylic acid copolymer NF, polysorbate 80 NF, sodium lauryl sulfate NF, and triethyl citrate NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Protonix is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.4 µg/mL, the time to reach the peak concentration (t_{max}) is 2.4 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 µg•hr/mL. When pantoprazole is given with food, its t_{max} is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6L.

Absorption

The absorption of pantoprazole is rapid, with a C_{max} of 2.5 µg/mL that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤ 23%) with once daily dosing.

Elimination

After a single oral or intravenous dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations

Geriatric

Only slight to moderate increases in pantoprazole AUC (43%) and C_{max} (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

Gender

There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (Also see Use in Women).

Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment

In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment.

Drug-Drug Interactions

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine (a CYP3A4 substrate), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2C9, 2D6 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Pharmacodynamics

Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+,K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of intravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown below.

Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH

	Median pH on day 7			
Time	Placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
\# Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20 and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups.

In long term studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin levels produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See **PRECAUTIONS**, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

Clinical Studies

PROTONIX Delayed-Release Tablets were used in all clinical trials.

Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)

A US multicenter double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n=541) in this study were as follows:

Erosive Esophagitis Healing Rates (per protocol)

	PROTONIX			Placebo
Week	10 mg QD (n = 153)	20 mg QD (n = 158)	40 mg QD (n = 162)	(n =68)
4	45.6%+	58.4%+#	75.0%+*	14.3%
8	66.0%+	83.5%+#	92.6%+*	39.7%

\+ (p < 0.001) PROTONIX versus placebo.
* (p <0.05) versus 10 mg, or 20 mg PROTONIX
\# (p <0.05) versus 10 mg PROTONIX

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 20-mg and 40-mg PROTONIX treatment groups. The 40-mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20- or 10-mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 20 mg and 40 mg once daily were also compared with nizatidine 150 mg twice daily in a US multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n=212) were as follows:

Erosive Esophagitis Healing Rates (per protocol)

	PROTONIX		Nizatidine
Week	20 mg QD (n = 72)	40 mg QD (n = 70)	150 mg BID (n = 70)
4	61.4%+	64.0%+	22.2%
8	79.2%+	82.9%+	41.4%

\+ (p < 0.001) PROTONIX versus nizatidine.

Once daily treatment with PROTONIX 20 or 40 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

INDICATIONS AND USAGE

Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

PROTONIX Delayed-Release Tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of PROTONIX may be considered.

The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. (see **PRECAUTIONS**).

CONTRAINDICATIONS

PROTONIX Delayed-Release Tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

In rodents, pantoprazole is carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these animal findings to humans is unknown. The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. PROTONIX is not indicated for maintenance therapy (see **INDICATIONS AND USAGE**).

Information for Patients
Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions
Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, or warfarin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy
Teratogenic Effects
Pregnancy Category B
Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Use in Women
Erosive esophagitis healing rates in the 221 women treated with pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

Use in Elderly
Erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS
Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two US controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

	% Incidence			
	Study 300-US		Study 301-US	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short-term domestic trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥ 1% in PROTONIX-treated patients: asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain, migraine, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting, hyperlipemia, liver function tests abnormal, SGPT increased, arthralgia, anxiety, dizziness, hypertonia, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, urinary frequency, and urinary tract infection.

In international short-term double-blind or open-label, clinical trials involving 20- to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
Study Event	Pantoprazole Total (N=2805)	Ranitidine 300 mg (N=594)	Omeprazole 20 mg (N=474)	Famotidine 40 mg (N=239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

Additional adverse experiences occurring in <1% of GERD patients based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, bilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports
There have been spontaneous reports of adverse events with the post-marketing use of pantoprazole. These reports include anaphylaxis; angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); and pancreatitis.

In addition, also observed have been jaundice, confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, and tinnitus.

Laboratory Values
In two US controlled trials, 0.4% of the patients on 40 mg pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE
Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg and 887 mg/kg were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION
Treatment of Erosive Esophagitis
The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered. (See **INDICATIONS AND USAGE**)

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of PROTONIX.

Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, chewed or crushed.

HOW SUPPLIED
PROTONIX is supplied as 40 mg yellow oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side.

They are available as follows:
NDC 0008-0841-10 bottles of 100
NDC 0008-0841-81 bottles of 90
NDC 0008-0841-91 bottles of 1000
NDC 0008-0841-99 carton of 10 Redipak® blister strips of 10 tablets each

Storage
Store PROTONIX Delayed-Release Tablets at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

℞ only

US Patent No. 4,758,579

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A Wyeth-Ayerst Company
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Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

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